Introduction to Skin

Introduction

In the module "The Cell" we discussed epithelia in general. We discussed the mechanisms behind intracellular connections in General Physiology, and then used those mechanisms to explain dysplasia and malignant transformation in Inflammation and Neoplasia. We now revisit these topics specifically in regard to the epithelium that is skin. This introductory lesson does review some of the same key points from those lessons, but the emphasis will be on the cell types and cell connections of skin as they relate to disease in subsequent lessons.

We start off with the arrangement of the **layers** of skin—the epidermis (the epithelium itself), the dermis (the extracellular matrix through which vessels traverse to the epithelium), and the hypodermis (the subcutaneous fat that separates the dermis from the muscle and bone below). Most of the discussion of this lesson is specifically in regard to the **strata** of the epithelium, zooming in only on the epidermis. The vocabulary can be confusing, so we do our best to simplify and be consistent. *Layers* will be used to reference the three layers that form the skin (epidermis, dermis, hypodermis). *Strata* will be used to reference the five layers of the epithelium (stratum basale, spinosum, etc.).

Layers of the Skin

The skin consists of three layers. The first is the epidermis, which contains the epithelial layer of living cells. The epi-dermis sits above the middle layer, the dermis. Below the dermis is the hypo-dermis. Hypo, below; epi, above.

The **epidermis** is the **epithelium** of skin, from the basement membrane to the apical surface. Think of the layer as being entirely **keratinocytes**, punctuated with melanocytes. The epidermis is the specialized, **keratinized** epithelium that is our skin. It is the waterproof barrier that protects the body from environmental pathogens and ensures that the moisture in the body doesn't evaporate. The epidermis consists of five strata—histologically distinct zones within that epithelium. The epidermis is the thinnest layer of skin, but the most densely packed with cells and metabolic activity. Blood is supplied to the epidermis from vessels coursing through the dermis. Imagine the epithelium, the densely packed coastal metropolis, next to a vast wasteland, the dermis.

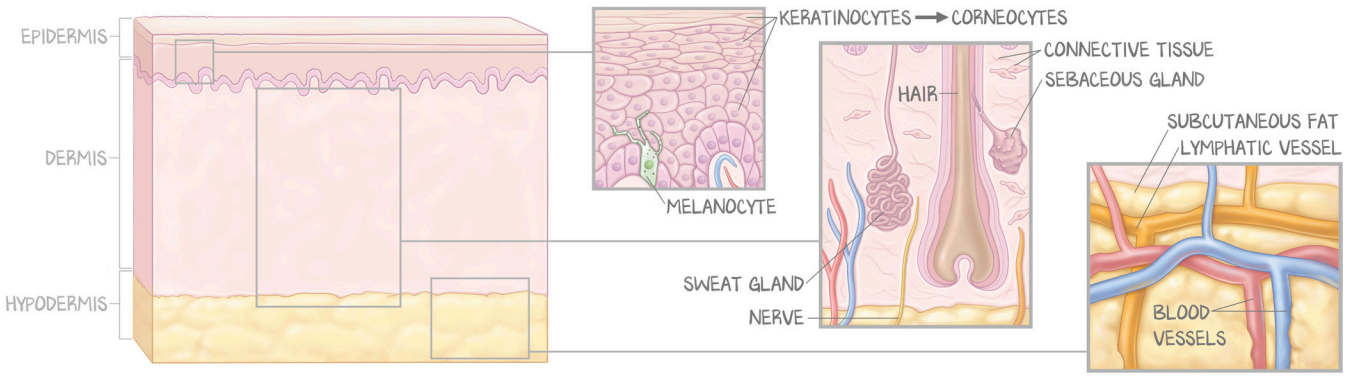


Figure 1.1: Layers of the Skin
The epidermis is the where the stratified squamous cells are. Here melanocytes provide pigment to the growing cell layer. Keratinocytes progressively differentiate to corneocytes, and are eventually sloughed off. The dermis is histologically massive relative to the epidermis. It is rather acellular, a connective tissue barrier between the pathogens outside the skin and the fat and muscle below. Blood vessels and nerves travel from the hypodermis to the epidermis through the dermis and appendages of the epidermis can be found within the dermis. The hypodermis is the subcunatenous adipose that sits above the fascia of the muscle and bone below and through which large vessels and nerves traverse.

The **dermis** is below the basement membrane of the epidermis and above the hypodermis. The dermis is the milieu of **connective tissue**, with collagen, elastic fibers, and fibroblasts. Through this sea of extracellular matrix run blood vessels, lymphatics, and nerves. Buried in the dermis, each with its own basement membrane to separate it from that sea of collagen, are sweat glands and sebaceous glands, glands that run from the dermis through the epidermis and out to the surface. All of the structures in the dermis either run to the skin surface (glands, hair) or from the adipose layer (vessels and nerves). This region of skin is enormous relative to the epidermis, and is mostly wasteland without nuclei or structures that take up histologic stain.

The **hypodermis** is the area of subcutaneous fat, consisting of adipocytes and more connective tissue. Through this layer are larger vessels that penetrate into the dermis. The hypodermis contacts the fascia and is more related to the muscles under the skin than it is to the dermis. When considering surgical closure, the hypodermis is the bottommost layer of skin. When considering histology of the epidermis, the adipose is so far away from the epidermis that we barely consider it.

Strata of the Epidermis

There are five strata of the epidermis, five histologically distinct zones of the epithelium of skin—stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum. We'll explore each stratum in the coming paragraphs. The concept is that at the basement membrane, at the bottom of the epithelium, stem cells divide and differentiate a daughter to a keratinocyte. As new keratinocytes are made, they push the rest of the epithelium one cell higher. As the keratinocyte moves toward the apical surface, it becomes further and further differentiated. Where it is made, it looks like the stem cell. As it ascends, it makes keratin. As it gets even higher, it degrades its organelles, including the nucleus, to make room for more keratin. At the very edge, in the stratum corneum, there are no nuclei, just giant sacs of keratin. That transition from densely-packed nucleus with little cytoplasm (basal cell) through metabolically active keratinocyte (squamous cell) into sac of keratin (still a squamous cell) is what this section is about. We'll use this information in Skin #4: *Skin and Soft Tissue Infections* and in Skin #6: *Inflammatory Dermatoses.*

First is the **stratum basale** (the basal cell layer; basale = basal; stratum = layer). The stratum basale contains the **basal cells**. The basal cells are the **stem cells**. The basal cells are also the ones that will become basal cell carcinoma. Because of their regular **mitotic activity**, these cells have **densely staining nuclei** and **scant cytoplasm**. The basal cells are held to the basement membrane by hemidesmosomes. Technically, only the stem cells are in contact with the basement membrane. The stratum basale is a histologic distinction and can be several cells thick. As long as the keratinocyte daughter looks like a basal cell, it is considered to be in the stratum basale, even though it is not a stem cell. The remaining cells of the stratum basale are the still-undifferentiated keratinocytes, the new daughters of mitosis. Being so young, they still express the histologic appearance of the stem cells.

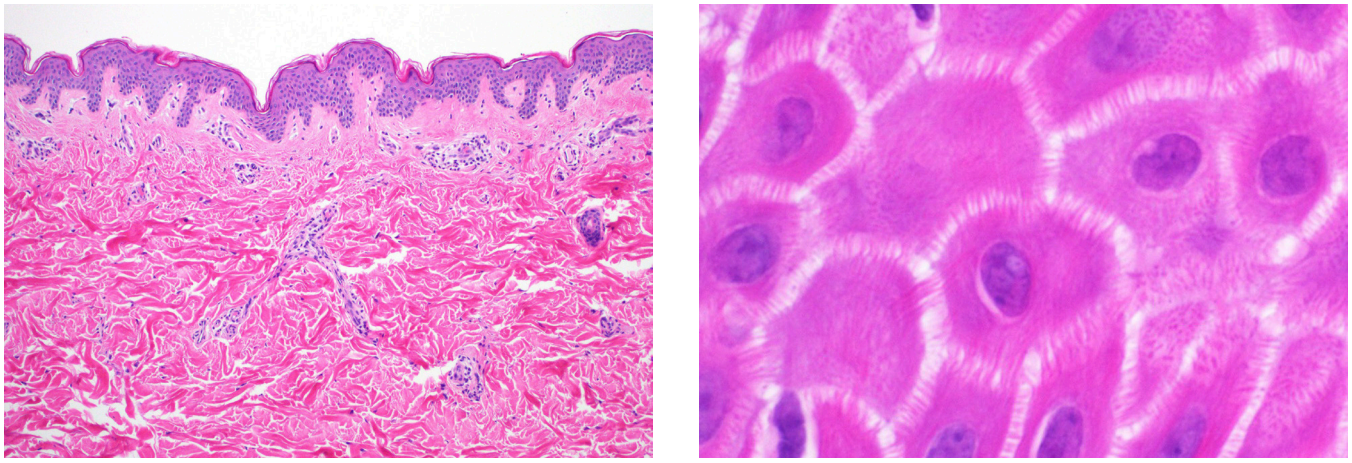
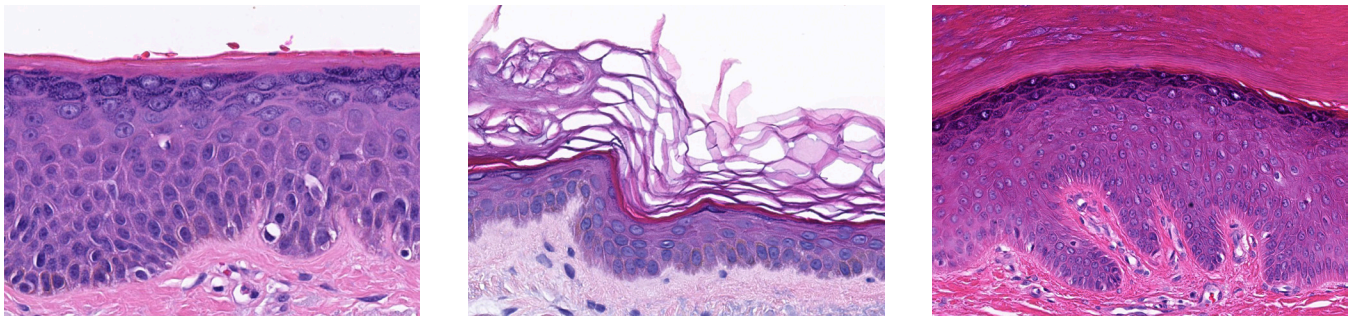


Figure 1.2: The Epithelium, Lower Strata
The epidermis, composed of stratified squamous epithelium, is at the top. The thin band of pale pink just beneath the epidermis is the papillary dermis. The remainder of the dermis is the reticular dermis, composed of large thick collagen bundles. A high magnification view of the stratum spinosum shows the numerous desmosomes ("spines") attaching each keratinocyte firmly to all of its neighboring keratinocytes. The keratinocytes have dense pink cytoplasm due to the abundant cytokeratin filaments they contain.

The majority of the epithelium is the **stratum spinosum** ("thorny layer"), named after the spiny projections connecting neighboring cells seen at high magnification on light microscopy. These connections are desmosomes. As the stem cell clones differentiate into keratinocytes, their **cytoplasm enlarges** and the nuclei do not stain as darkly. The cellular machinery is being turned on (cytoplasm enlarges), proteins are transcribed (DNA needs to be euchromatin), and the cells will never divide again (nucleus never needs to condense again). These keratinocytes continue to differentiate, turning on the genes required to make keratin. In the spinosum, they also begin making keratin.

The **stratum granulosum** ("granular layer") gets its name from the histologic appearance of **granules**. As that cellular machinery revs up, keratinocytes make **keratin filaments** and a protein called filaggrin, which holds the filaments together. These are first packaged into keratin granules. The nuclei are still active, and the cell still has cellular architecture, but the histologic appearance is that of **darkly basophilic** cytoplasm, from all the **keratohyalin granules**.

As the cell approaches terminal differentiation, transitioning from the stratum granulosum to the stratum corneum, membrane-bound organelles begin to disappear. The enucleated keratinocyte is now a corneocyte (cool word, rarely used). The corneocyte is very much alive and now terminally differentiated—it is not dead nor undergoing apoptosis. Just as a red blood cell has no nucleus or mitochondria and is filled with hemoglobin, a skin cell has no nucleus or mitochondria and is filled with keratin.



(a) (b) (c)

Figure 1.3: The Epithelium, Upper Strata
In the stratum granulosum, keratinocytes accumulate numerous purple keratohyaline granules in their cytoplasm. Keratinocyte nuclei are still intact in this strata. (b) The stratum corneum in normal skin is composed of terminally differentiated corneocyte without retained nuclei. In thin skin, the keratin often has a loose "basketweave" pattern as shown here. In thick acral skin (palms/soles), the stratum corneum is a lot thicker and its keratin is denser and more tightly packed together as in the next slide. (c) The stratum lucidum is the thin pale pink band seen here dividing the purple stratum granulosum from the dense pink stratum corneum. The stratum lucidum is usually only visualized microscopically in acral skin.

The final stratum is the **stratum corneum** ("horny layer"). By this stage the nuclei are gone, the nucleus and cytoplasmic organelles disrupted and filled with keratin. These represent the most differentiated form of keratinocyte. They are mostly membrane-bound sacs of keratin held to each other by desmosomes, without much other cellular machinery. These cornified, thickened cells are what we think of as our skin, the thing we see with our eyes. This stratum does the protecting—prevents water from leaving and prevents pathogens and debris from getting into the epithelial layer below.

The thickness of any skin epithelium is determined by how many cells are still attached at the stratum corneum—all skin epithelia have about the same sized stratum basale, spinosum, and granulosum. The only stratum that varies in size is the corneum. More cells, thicker stratum corneum, thicker skin. The stratum thickness can vary because the cells are still alive. Even though their nucleus is not visible, enzymatic activity progresses. Without mitochondria, these cells develop cytoplasmic lactic acid, and the pH drops.

The farther out the cells are from the basement membrane, the longer they've been alive, and the farther they get from the oxygen delivery in the dermis. Keratinocytes are held together by **desmosomes**. The topmost keratinocytes (corneocytes) fall off because of **desquamation**, a programmed proteolytic cleavage of the desmosomes. Both the presence of these enzymes and the pH of the cell determine the rate at which the desmosomes are lost. The transcription rate of the gene that codes these proteolytic enzymes during differentiation determines how long the corneum will hold on. Cells that transcribe more proteolytic enzymes in the stratum spinosum will degrade desmosomes between these cells in the stratum corneum faster, and they desquamate faster, making the skin thin. Cells that transcribe fewer proteolytic enzymes in the stratum spinosum will degrade desmosomes between these cells in the stratum granulosum slower, and therefore "hold on" longer, making thicker skin.

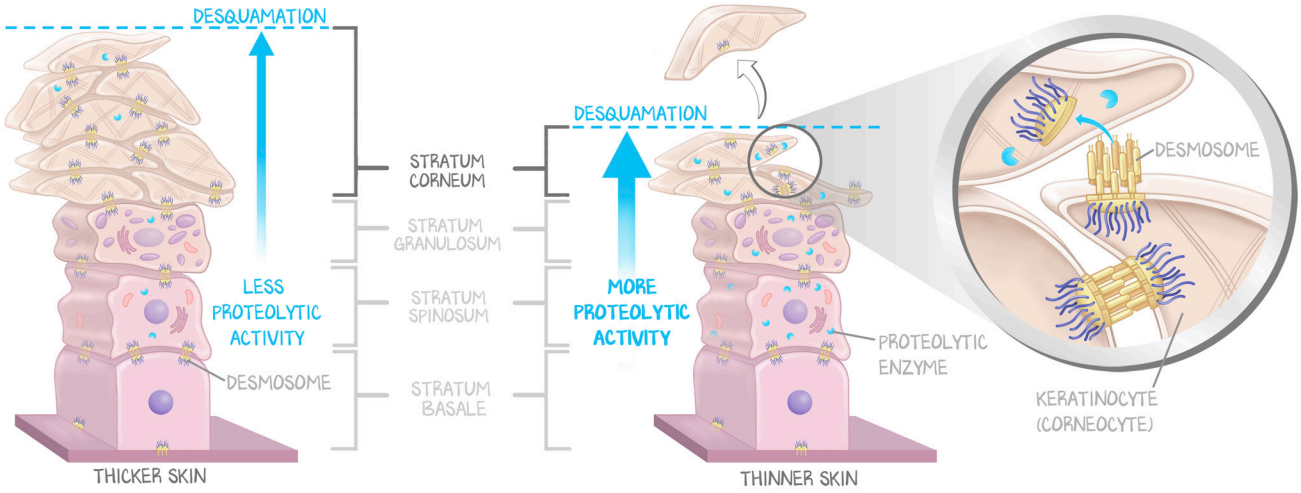
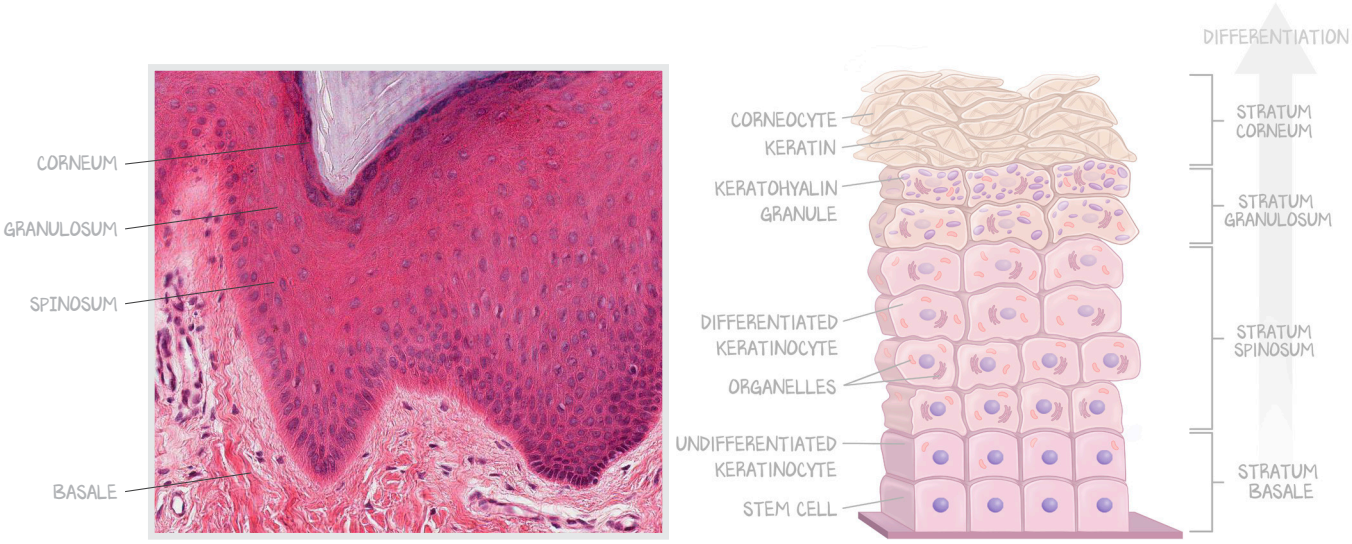


Figure 1.4: Desmosomes and Proteolytic Activity Leading to Thicker Skin
The thickness of skin is determined by proteolytic activity in corneocytes. As a keratinocyte—with a nucleus, ribosomes, and an endoplasmic reticulum—the cell chooses how much enzyme to make. Those of thin skin make a lot of enzyme. Those of thick skin make less. That enzyme cleaves desmosomes from the inside, releasing the connection that cell has to the rest of the cell layer.

The **stratum lucidum** ("clear layer") is between the granulosum and corneum. We teach it out of order because some histologists classify it as a subdivision of the corneum, while others see it as its own stratum. It is present only in thick skin. It represents a visualization of the transition from obviously granulosum (nuclei intact, keratin not filling all organelles) to obviously corneum (nuclei gone, keratin everywhere). That transition happens regardless. It's just that in really thick skin, that transition may be visible on light microscopy as a distinct stratum.



(a) (b)

Figure 1.5: The Layers and Cells of the Epidermis
(a) Moderate-zoom view of the epithelial layer, with strata labeled. (b) Artist's rendition of the cell's progression through the layers of skin, demonstrating the progression from darkly staining nuclei of the cuboid basal cells to the squamous with less-well-staining nuclei and abundant granular cells, into the nuclei-less, keratin-filled corneum.

Skin, Hair, and Nails

We go into the details of the dermis-related structures in MSK #18: *Appendages of Skin*. The keratohyaline and keratin granules of skin give rise to **soft keratin**. This ensures that our skin is malleable. It serves as a barrier to prevent pathogen entry and to prevent water evaporation from the organs beneath, but it is soft, loose.

In comparison, **nails** and **hair** do essentially the same thing as skin—stem cells in the stratum basale produce keratinocytes which differentiate into corneocytes filled with keratin. As new cells are added to the base of the epithelium, the rest of the cells are pushed one cell layer higher. This is how nails and hair grow. Two very different things happen to the corneocytes of **hard keratin**. First, they **do not desquamate**, which is why you must trim your nails and why you visit a hair salon. Second, they **do not form keratin granules**. Instead, they are made of a keratin that is different from skin, and the details are not worth learning.

The point, though, is that skin, hair, and nails are essentially the same process. Soft keratin desquamates and makes granules. Hard keratin does not.

Histologic Dermatopathology

We wanted to introduce the following terms here. As we go through the Skin series, we will engage them in detail in regard to the disease that causes them.

Hyperkeratosis is a thickening of the stratum corneum. Thickening of the stratum corneum means more keratinocytes hang on longer. This happens in thicker skin, such as develops when callouses develop, in response to thin skin trauma (like playing a guitar). This also happens when there is induction of skin cell proliferation, as occurs in psoriasis or in response to dermatophyte infestation. **Parakeratosis** is the persistence of nuclei in the stratum corneum. There should be no nucleated cells in the stratum corneum. The presence of nuclei indicates either that the cells aren't behaving the way they should (cancer) or that the proliferation of keratinocytes has been increased. Thus, in conditions like psoriasis or dermatophyte infestation, you may see hyperkeratosis (thicker keratin layer) with parakeratosis (nuclei in the corneum).

Hypergranulosis is well named, and is simply an enlargement of the stratum granulosum. It is only relevant in lichen planus, which we will discuss later in this module. **Spongiosis** is fluid accumulation, edema, within the epidermis. This will appear as white and will distort the epidermal layer.

Acanthosis is hyperplasia of the epidermis, usually an enlargement of the spinosum layer. You would think that this would raise the skin, push the corneum higher. But instead, epidermal hyperplasia results in the epithelium's growth into the dermis—the keratinocytes will be farther "down" into the dermis. They are still lined by a basement membrane; the basal cells are simply farther from the corneum.

Acantholysis is the loss of contact between keratinocytes. More on this in the lesson on bullous diseases.

Skin Lesion Descriptions

A flat lesion, one that is continuous with the skin around it and is not palpable as being something different, is called a **macule** when small (< 1 cm) and a **patch** when large (> 1 cm). Flat lesions are flat, and so are generally not filled with anything or displaced by other tissue. A raised lesion, one that is visually and tactilely different from the skin around it, is called a **papule** when small (<1cm) and a **plaque** when large (> 1 cm). Raised lesions are usually normal on top (what the person can see) and are induced by proliferation or deposition under or within the epidermis. A fluid-filled lesion (a blister) is either a **vesicle** when small (< 1 cm) or a **bulla** (plural bullae) when large (> 1 cm). A break in the skin can be defined as a **fissure** (narrow tear into the dermis), an **erosion** (shallow tear into epidermis), or an **ulcer (**wide tear through epidermis into dermis).

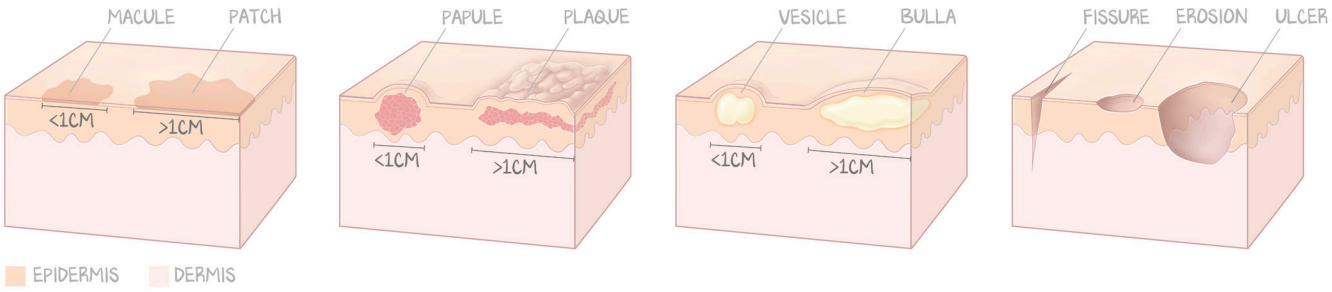


Figure 1.6: Skin Lesion Descriptions
This serves as a visual representation of the text that precedes it.

Cells of the Epidermis

The cells of the epidermis are discussed in various detail in different sections of this course. We'll use this information in Skin #2: *Skin Cancers* and Skin #5: *Disorders of Skin Pigmentation.* The **keratinocytes** are described in the section above. The distinction between **basal cell** (stem cell, undifferentiated, stratum basale, cuboid to columnar shape) and **squamous cell** (keratinocyte, differentiated, stratum spinosum/granulosum/corneum, squamous shape) is important for cancers. These are the cells that will be involved in most diseases of the skin. Basal cells give rise to basal cell carcinoma. Squamous cells give rise to squamous cell carcinoma. Both squamous cells and basal cells are keratinocytes.

Melanocytes (not keratinocytes at all) are the other cell type of significant importance to this dermatopathology section of the course. The melanocytes make melanin. They are staggered along the basal layer with long projections into the stratum basale. These cells contain organelles called melanosomes, which **synthesize melanin** from tyrosine. The melanocytes then transfer melanin from melanosomes into the newly formed keratinocytes through dendritic processes. The lipid double bilayer of the melanosome fuses with the lipid double bilayer of the melanocyte cell membrane, which fuses with the lipid double bilayer of a keratinocyte, which then buds off to form a membrane-bound organelle with melanin in the keratinocyte. The more melanin that gets made—melanocyte activity, not melanocyte number—the darker the skin. Any **disorder of skin pigment is a disorder of melanocytes**. Hypopigmentation can be caused by melanin production dysfunction or loss of melanocyte number. Excess proliferation of melanocytes gives rise to nevi and melanoma.

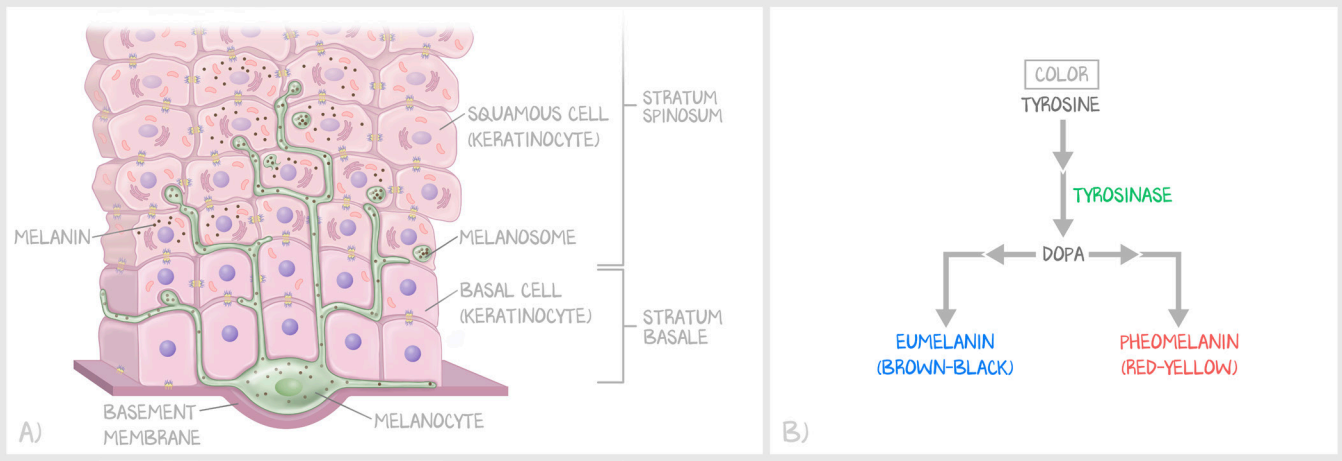


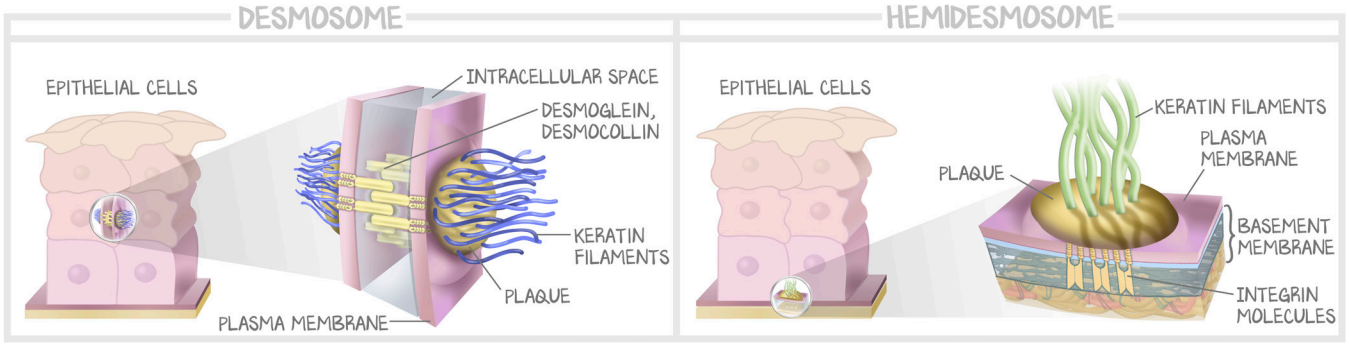
Figure 1.7: Cells of the Epidermis
(a) Melanocytes are present in the stratum basale and provide pigment—melanin—to nacent keratinocytes via melanosomes. (b) Melanin is synthesized from tyrosine. One critical step involves tyrosinase. Melanin can be either eumelanin or pheomelanin. The combination of the two pigments determines skin color.

Other cells of the epidermis are mentioned here for completeness. Langerhans cells are the antigen-presenting cells of the epithelium and are involved in host defense of invading pathogens. This is all we will say about them. Merkel cells are mechanoreceptors, which we discuss in special senses under Neurology. For our discussion on skin, there are basal cells, squamous cells, and melanocytes, that's it.

Epithelial Cell Connections

These were discussed in detail in the General Physiology: *Epithelium* lesson. The ones we need for dermatopathology are reviewed briefly here—desmosomes and hemidesmosomes. We'll use this information in the Blistering diseases *Skin #3: Blistering Diseases*.

Desmosomes, also known as **maculae adherentes** (singular: macula adherens) are how the cells of an epithelium stay physically connected to each other. Desmosomes are spot-welds that fasten cells to each other. A desmosome is a *macula* (Latin for "spot, stain"), not forming a *zona* (Latin for "belt"), and so desmosomes are found punctuating the lateral domain and NOT as a band around the cell. **Desmoglein** or desmocollin (extracellular cadherins) interact with desmoglein or desmocollin on a neighboring cell, forming an extracellular anchor. On either neighboring cell is an intracellular plaque, made of **desmoplakin**, which, together with intermediate filaments, forms the intracellular anchor. Together, the plaques and cadherins form a strong bond between neighboring cells. When each cell is anchored to a neighbor, the net effect is one common wall of cells connected by strong bonds. Without desmosomes, the cell-to-cell contact would fail, and the cells of a layer would drift apart.



(a) (b)

Figure 1.8: Epithelial Junctions
(a) The desmosome is the connection between all cells of an epithelium. It consists of extracellular cadherin molecules, intracellular plaques, and cytoplasmic intermediate filaments connecting it to the cytoskeleton. (b) The hemidesmosomes are the connection between the cells of the stratum basale, between the stem cells and the basement membrane. Only the stem cells have this connection, and are connected to the rest of the layer by desmosomes. Hemidesmosomes are made of extracellular integrin molecules, intracellular plaque, and cytoplasmic actin filaments.

Hemidesmosomes connect the stem cells of the stratum basale to the basement membrane. The daughters of proliferation that histologically belong to the stratum basale and which will differentiate into squamous cells are not attached to the basement membrane but instead are attached to each other by desmosomes. The hemidesmosome is the anchor of the entire epithelial layer to the extracellular matrix. The ECM connects to the basement membrane. The stem cells of the stratum basale connect to the basement membrane via hemidesmosomes. The stem cells connect to the squamous cells via desmosomes. Every keratinocyte connects to another with desmosomes. Hemidesmosomes connect only the bottom row of cells to the basement membrane. Hemidesmosomes use **extracellular integrin** molecules that interact with the ECM and an **intracellular plaque**.

Citations

Figures 1.2a, 1.2b, 1.3a, 1.3b, 1.3c: Courtesy of Jerad M. Gardner, MD.

Figure 1.2a: Originating from the University of Alabama at Birmingham, Department of Pathology PEIR Digital Library at http://peir.net pursuant to a license grant by the UAB Research Foundation.